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| EXAMINER |
|---|
| WILSON, MICHAEL C |

| ART UNIT | PAPER NUMBER |
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| 1632 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/649,859 | Applicant(s) Berg |
|---|---|---|
| | Examiner Michael C. Wilson | Art Unit 1632 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *11-28-02 and 12-6-02* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-7* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *4, 5*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

Applicant's arguments filed 11-28-02, paper number 10, have been fully considered but they are not persuasive. The five declarations filed 11-28-02 in paper number 10, and the one declaration filed 12-6-02, paper number 11, have been considered but are not persuasive as discussed below. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 8 and 9 have been canceled. Claims 1-7 are pending and under consideration in the instant office action.

### *Specification*

1. The disclosure is objected to because of the following informalities: the first line of the specification needs updated to reflect the status of the applications and to include all of the applications to which priority is claimed.

Appropriate correction is required.

### *Claim Objections*

2. Claim 3 as newly amended is objected to because of the following informalities: the phrase "collagen or a pro-α1 chain" should be --collagen, and a pro-α1 chain-- to be in proper Markush format. Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

3. Claims 1-7 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid sequence encoding human procollagen operably linked to a promoter that functions in mammary glands, a fertilized mammalian egg or a mouse ES cell comprising a nucleic acid sequence encoding human collagen operably linked to a promoter that functions in mammary glands, a non-human mammal whose genome comprises a nucleic acid sequence encoding human collagen operably linked to a promoter that functions in mammary glands, wherein said mammal secretes human collagen into its milk and a method of preparing human collagen comprising recovering milk for said transgenic non-human mammal, and recovering human collagen from the recovered milk, does not reasonably provide enablement for any fertilized non-human egg or embryonic stem cell as broadly claimed or for a mammal further modified to contain an expression system that effect the production of post-translational modification enzymes for procollagen as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

The specification does not enable any fertilized non-human egg having the construct claimed (claim 4). The construct is used to produce proteins in the milk of transgenic mammals. However, the eggs claimed encompass any non-human animal. Non-mammalian animals do not have mammary glands. The specification does not teach how to use non-mammalian eggs having a construct with a mammary-gland specific promoter. As such, it would require one of skill

undue experimentation to determine how to use non-mammalian fertilized eggs having a construct that expresses proteins in mammary glands.

The specification does not enable any non-human ES cells as broadly claimed (claim 5). Krimpenfort taught making transgenic bovines expressing proteins in their milk using fertilized oocytes displaying germline transmission of transgenes (1991, Bio/Technology, Vol. 9, pg 844-847). Krimpenfort did not use bovine ES cells. In fact, Mullins (1996, J. Clin. Invest., Vol. 98, pages S37-S40) taught that ES cells providing germline transmission were only available in mice (pg S38, col. 1, para. 1). Therefore, the art at the time of filing and the specification does not teach how to make ES cells that provide germline transmission other than mouse ES cells. The specification does not correlate methods of isolating mouse ES cells that provide germline transmission to other methods of isolating other species of ES cells that provide germline transmission. Given what was known in the art taken with the teachings in the specification, it would have required one of skill undue experimentation to obtain a non-human ES cell other than a mouse ES cell.

The specification does not enable a transgenic non-human mammal merely comprising the expression system as claimed (claim 6). The expression system must be passed through the germline (see Krimpenfort, pg 844, col. 1, para. 1) which requires that the construct is part of the genome of the mammal for protein expression to occur. The art at the time of filing did not teach how to obtain protein expression in milk without the construct being a part of the genome. As

such, the claims should be limited to non-human mammals whose genomes comprise the construct.

In addition, claim 6 is not enabled as broadly claimed because it does not recite the phenotype of the non-human mammal. The specification does not provide an enabled use for a transgenic comprising the construct that does not produce procollagen or collagen in its milk. As written, the claims do not clearly set forth that protein is expressed in the milk. A positive, clear statement indicating the phenotype of the mammal would overcome this rejection.

The specification does not enable a mammal having a second construct that effects production of post-translational modification enzymes for procollagen as claimed (claim 7). The art at the time of filing was that the phenotype of transgenic mice was unpredictable because of the variability of transgene expression (Mullins above; pg S37, col. 2, line 7). In addition, Wall (1996, Theriogenology, Vol. 45, pages 57-68) taught transgene expression and the physiological result of such expression in livestock was not always accurately predicted in transgenic mice (page 62, line 7). The specification contemplates using such constructs in combination with constructs encoding procollagen (pg 16, line 8; pg 17, line 6; pg 18, line 1). In particular, the specification describes methods of producing both constructs in the same animal by putting both constructs in at the same time or by producing two separate transgenic animals that are bred to combine the constructs (pg 19, line 16 through pg 21, line 7). The guidance provided in the specification is inadequate to overcome the unpredictability in the art. The specification states expression of both of the enzymes must occur together because the enzymes function together as

a tetrameric protein (pg 21, line 1). The specification does not teach the expression of any enzymes in the milk of transgenic mammals. The specification does not provide adequate guidance such that the expression of both enzymes is the same, that the enzymes are capable of forming a tetrameric protein or that the amount of tetrameric protein obtained is capable of post-translational processing of procollagen. In addition, the α-subunit of prolyl hydorxylase has not yet been completely described or sequenced (pg 10, line 3, of the specification). Without such guidance, taken with the unpredictability in the art for one of skill to obtain a phenotype of interest, it would have required one of skill undue experimentation to obtain the mammal claimed.

Applicants point to the six declarations which, applicants argue, support enablement for the claimed invention. Applicants have not provided any arguments specific to the breadth of any fertilized non-human egg or embryonic stem cell as broadly claimed or for a mammal further modified to contain an expression system that effect the production of post-translational modification enzymes for procollagen as claimed. The declarations are not persuasive. The first declaration by David Toman is directed toward "the Meade reference" which is not of record. The second and third declarations by David Toman are identical and do not address the breadth of any fertilized non-human egg or embryonic stem cell as broadly claimed or for a mammal further modified to contain an expression system that effect the production of post-translational modification enzymes for procollagen as claimed. The fourth and fifth declarations by David Toman do not address the breadth of any fertilized non-human egg or embryonic stem cell as broadly claimed or for a mammal further modified to contain an expression system that effect the

production of post-translational modification enzymes for procollagen as claimed. The declaration by Scott Leigh filed 12-06-02, paper number 11, addresses separating collagen types from collagen mixtures and does not correlate to the enablement rejection.

4. Claims 1-7 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

The rejection of claims 1, 4, 7 regarding "containing" is withdrawn in view of the amendment.

Claim 1 remains indefinite because the phrase "coding nucleotide sequence encoding at least one human procollagen operably linked to control nucleotide sequences that effect expression specifically in milk protein-secreting epithelial cells of said mammary glands under conditions wherein said coding nucleotide sequence is expressed to secrete human procollagen..." is unclear. It is unclear if "specifically" means "exclusively" or "mostly". It is unclear if procollagen expression occurs in the milk because it is unclear whether the "conditions" as claimed actually occur. The claim does not clearly set forth the description of the regulatory element or the step of obtaining protein expression or secretion in the milk.

The aspect of the phrase regarding "effect" is withdrawn as "effect" means "to bring into existence, to produce as a result, or to bring about" (www.bartleby.com/61/ ; enter "effect").

Applicants argue that "tissue-specific expression" is an art-recognized term to distinguish non-specific protein expression. Applicants argue that some "leakage" or basal expression

outside of the targeted tissue is allowed. Applicants argument is not persuasive. Applicants have not provided any art-recognized definition of "tissue-specific expression" or any evidence that some "leakage" or basal expression outside of the tissue of interest is allowed. In addition, how much leakage is allowed outside of the tissue of interest before the expression is no longer considered "tissue-specific"? As such, the metes and bounds of "expression specifically in milk protein-secreting epithelial cells" cannot be determined. Applicants have not addressed how the phrase "under conditions wherein said coding nucleic acid is expressed to secrete human procollagen..." further limits the claim. It is unclear if applying the "conditions" are an active step in the method, whether the "conditions" occur, what the "conditions" are, and to what the "conditions" are applied. As written, it is unclear whether the phrase refers to the control nucleotide sequence, the epithelial cells or the mammary glands. The phrase --a nonhuman mammal whose genome comprises an expression system comprising a nucleic acid sequence encoding at least one human collagen operably linked to a promoter that functions in milk protein-secreting epithelial cells, wherein said at least one human collagen is expressed and secreted into milk of said mammal-- would be clear.

Claim 1 remains indefinite because the steps of the claim are not in a logical order. The step of recovering milk should be after obtaining secretion of the protein in the milk and before recovering protein from the milk.

Applicants argue the milk is isolated then the protein is isolated from the milk; therefore, applicants argue the steps of the claim are properly ordered. Applicants argument is not

persuasive. Expression and secretion into the milk is essential to the invention and does not occur in the claim until after the milk is isolated which does not make sense, especially in view of the fact that the claim may require steps or "conditions" which cause expression of the protein in the milk. If applicants wish to merely describe the structure of the nonhuman mammal in first step as --isolating milk from a nonhuman mammal whose genome comprises an expression system comprising a nucleic acid sequence encoding at least one human collagen operably linked to a promoter that functions in milk protein-secreting epithelial cells, wherein said at least one human collagen is expressed and secreted into milk of said mammal--, that would be acceptable; however, as written, the "isolating milk" steps appears to encompass other method steps which is confusing.

Claims 1 and 2 remain indefinite because the use of the word "coding" to describe a nucleotide sequence encoding a protein is redundant. Applicants argue it distinguishes non-coding sequences. Applicants argument is not persuasive. The nucleotide sequence encoding a protein distinguishes non-coding sequences. How does the term "coding" further limit a "nucleotide sequence encoding a protein"? Deleting "coding" would overcome this rejection.

The rejection of claim 3 regarding "the pro-α1 chain" is withdrawn in view of the amendment.

Claim 7 remains indefinite because it does not clearly set forth the structure or function of the expression system. The claim does not require that the system encodes an enzyme; it only has

to "effect" the production of enzymes. The claim does not require that the enzyme function occurs or that procollagen is cleaved to form collagen. As such, the claim as written is unclear.

Applicants argue "effect" is "to cause". Applicants argument is misplaced because it is unclear whether the expression system encodes the enzyme or some other protein that causes expression of the enzyme.

***Claim Rejections - 35 USC § 103***

5. Claims 2-3 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Buhler (Feb. 1990, Biotechnol., Vol. 8, pg 140-143) in view of Khillan (Dec. 5, 1991, J. Biol. Chem., Vol. 266, pg 23373-23379) for reasons of record.

Buhler taught a construct comprising a nucleic acid sequence encoding a protein operably linked to the β-casein promoter for producing the protein in the milk of transgenics (pg 143, col. 2, "Construction..."). Buhler taught fertilized eggs comprising a construct comprising a nucleic acid sequence encoding a protein operably linked to the β-casein promoter (pg 143, col. 2, "Construction..."). The fertilized eggs were transplanted into pseudopregnant females and transgenics comprising the transgene were obtained ("Generation..."). The protein was expressed and secreted in the mammary gland of the transgenics and isolated from the milk (pg 141, col. 1, "Tissue specific transcription..."). The fertilized eggs of Buhler become blastocysts which inherently comprise ES cells as claimed because the fertilized eggs were 19.5 hours post-fertilization at which time ES cells occur ("Generation..., line 2). Buhler did not teach the

construct encoded procollagen. However, Khillan taught a construct for expressing the pro-α1 chain of Type I collagen in transgenics.

Thus, it would have been obvious to one of skill in the art at the time the invention was made to make a construct encoding a protein operably linked to the β-casein promoter as taught by Buhler wherein the protein was the pro-α1 chain of Type I collagen as taught by Khillan. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the protein taught by Buhler with the pro-α1 chain of Type I collagen to produce the pro-α1 chain of Type I collagen in the milk of transgenics. One of ordinary skill in the art at the time the invention was made would have recognized that the transgenic described by Buhler was a bioreactor and would have been motivated to make any protein in the bioreactor. One of ordinary skill in the art at the time the invention was made would have been motivated to direct expression of human procollagen to the mammary gland of the transgenic to prevent a systemic immune response to the human protein. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in obtaining pro-α1 chain of Type I collagen expression in mammary glands because Buhler obtained exogenous protein secretion in the mammary glands of transgenics, and because Khillan obtained human pro-α1 chain of Type I production in transgenics. The combined teachings of Buhler and Khillan are no less than the specification which merely suggests making animals using methods known in the art and using the pro-α1 chain of Type I collagen (pg 13, line 26).

Applicants argue collagen is much bigger than smaller globular proteins known to be produced in milk at the time of filing. Applicants argue that collagen had not been produced in cells that did not already produce collagens. Therefore, applicants apparently conclude that one of ordinary skill in the art at the time the invention was made would not have had a reasonable expectation of success in obtaining collagen expression in the milk. Applicants arguments are not persuasive. Khillan (1991, J. Biol. Chem., Vol. 266, pg 23373-23379) taught obtaining transgenic mice expressing collagen tissues that did not normally express collagen (see pg 23375, col. 2, Fig. 1, which shows collagen expression in tails and intestines). Therefore, one of ordinary skill in the art would have had a reasonable expectation of success in obtaining collagen expression in a tissue that did not normally express collagen as taught by Khillan. One of skill would have had a reasonable expectation of successfully expressing collagen in breast tissue because other globular proteins, though not as large, had been expressed in the breast tissue and because collagen had been expressed in tissue that did not normally express collagen. Expression of collagen in the milk would cause any phenotypic alteration in the animal which is considered a bioreactor and is not affected by protein expression in the milk. Furthermore, "for production... ...in milk" in claim 2 does not bear patentable weight because it is an intended use which may not occur. One of ordinary skill in the art would have had a reasonable expectation of merely combining the nucleic acids required to make the expression system of claim 2 and make the egg and ES cell of claims 4 and 5.

6. Claims 1, 2 and 4-6 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Buhler (Feb. 1990, Biotechnol., Vol. 8, pg 140-143) in view of Lee (1988, J. Biol. Chem., Vol. 263, pg 13414-13418) for reasons of record.

Buhler taught a construct comprising a nucleic acid sequence encoding a protein operably linked to the β-casein promoter for producing the protein in the milk of transgenics (pg 143, col. 2, "Construction..."). Buhler taught fertilized eggs comprising a construct comprising a nucleic acid sequence encoding a protein operably linked to the β-casein promoter (pg 143, col. 2, "Construction..."). The fertilized eggs were transplanted into pseudopregnant females and transgenics comprising the transgene were obtained ("Generation..."). The protein was expressed and secreted in the mammary gland of the transgenics and isolated from the milk (pg 141, col. 1, "Tissue specific transcription..."). The fertilized eggs of Buhler become blastocysts which inherently comprise ES cells as claimed because the fertilized eggs were 19.5 hours post-fertilization at which time ES cells occur ("Generation..., line 2). Buhler did not teach the construct encoded procollagen.

However, Lee taught a construct for expressing human Pro-α2(I) collagen, transfecting liver cells with the construct and obtaining functional expression of Pro-α2(I) collagen (pg 13414, col. 2, 2nd para.).

Thus, it would have been obvious to one of skill in the art at the time the invention was made to make a construct encoding a protein operably linked to the β-casein promoter as taught by Buhler wherein the protein was Pro-α2(I) collagen as taught by Lee. One of ordinary skill in

the art at the time the invention was made would have been motivated to replace the protein taught by Buhler with the Pro-α2(I) collagen of Lee to produce Pro-α2(I) collagen. One of ordinary skill in the art at the time the invention was made would have recognized that the rabbit described by Buhler was a bioreactor and would have been motivated to make any protein in the bioreactor. One of ordinary skill in the art at the time the invention was made would have been motivated to direct expression of human Pro-α2(I) collagen to the mammary gland to prevent a systemic immune response to the human protein. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in obtaining Pro-α2(I) collagen expression and secretion in mammary glands because Buhler obtained exogenous protein from the milk of the rabbits and because Lee obtained Pro-α2(I) expression in cells that do not normally produce collagen. The combined teachings of Buhler and Lee are no less than the specification which suggests making animals using methods known in the art and using the Pro-α2(I) collagen of Lee (pg 13, line 26).

Applicants arguments regarding 103 are generic to all of the 103 rejections. Applicants arguments are not persuasive for reasons addressed above.

7. Claims 2-6 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Krimpenfort (1991, Bio/Technology, Vol. 9, pg 844-847) in view of Khillan (Dec. 5, 1991, J. Biol. Chem., Vol. 266, pg 23373-23379) for reasons of record.

Krimpenfort taught a construct comprising a nucleic acid sequence encoding a protein operably linked to the αS1-casein 5' and 3' regulatory regions (pg 845, Fig. 1). The construct was

injected into fertilized eggs (pg 845, col. 2, line 18). The fertilized eggs were transplanted into pseudopregnant female bovines and transgenic offspring were obtained (pg 8846, col. 1, "DNA analysis"). The fertilized eggs comprise ES cells as claimed because the fertilized eggs were injected with the construct between 18-23 hours after fertilization which divides and inherently produce ES cells within the embryo. Krimpenfort does not expressly teach obtaining protein expression in the mammary gland or isolating the protein from the milk; however, claim 6 does not require the transgenics secrete protein in their mammary gland. It is noted that Krimpenfort taught the purpose of obtaining the transgenics was to express the protein in their mammary gland (pg 844, col. 2, line 7-10). Krimpenfort did not teach the construct encoded procollagen or the transgenic bovine comprised a construct encoding procollagen.

However, Khillan taught a construct encoding the human pro-α1 chain of Type I collagen, transfecting liver cells with the construct and obtaining functional expression of the pro-α1 chain of Type I collagen in transgenic mice.

Thus, it would have been obvious to one of skill in the art at the time the invention was made to make a construct encoding a protein operably linked to the αS1-casein regulatory regions as taught by Krimpenfort wherein the protein was the pro-α1 chain of Type I collagen as taught by Khillan. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the protein taught by Krimpenfort with the pro-α1 chain of Type I collagen taught by Khillian to produce the pro-α1 chain of Type I collagen in a bioreactor. One of ordinary skill in the art at the time the invention was made would have recognized that the bovine

described by Krimpenfort was a bioreactor and would have been motivated to make any protein in the bioreactor. One of ordinary skill in the art at the time the invention was made would have been motivated to direct expression of human procollagen to the mammary gland to prevent a systemic immune response to the human protein. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in obtaining Pro-α2(I) collagen expression in mammary glands because Krimpenfort obtained exogenous protein expression in mammary glands of transgenics and because Khillan obtained pro-α1 chain expression in transgenics. The combined teachings of Krimpenfort and Khillan are no less than the specification which suggests making animals using the method of Krimpenfort (pg 10, line 19) and using the pro-α1 chain of Type I collagen.

Applicants arguments regarding 103 are generic to all of the 103 rejections. Applicants arguments are not persuasive for reasons addressed above.

8. Claims 2-6 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Krimpenfort (1991, Bio/Technology, Vol. 9, pg 844-847) in view of Lee (1988, J. Biol. Chem., Vol. 263, pg 13414-13418) for reasons of record.

Krimpenfort taught a construct comprising a nucleic acid sequence encoding a protein operably linked to the αS1-casein 5' and 3' regulatory regions (pg 845, Fig. 1). The construct was injected into fertilized eggs (pg 845, col. 2, line 18). The fertilized eggs were transplanted into pseudopregnant female bovines and offspring comprising the transgene were obtained (pg 8846, col. 1, "DNA analysis"). The fertilized eggs inherently comprise ES cells as claimed because the

fertilized eggs were injected with the construct between 18-23 hours after fertilization which divides to produce ES cells within the embryo. The claim does not require obtaining expression in the mammary gland (see 112/2nd); however, Krimpenfort teaches the purpose of obtaining the offspring was to express the protein in their mammary gland (pg 844, col. 2, line 7-10). Krimpenfort did not teach construct comprised procollagen or the transgenic bovine comprised a construct encoding procollagen.

However, Lee taught a construct for expressing Pro-α2(I) collagen, transfecting liver cells with the construct and obtaining functional expression of Pro-α2(I) collagen (pg 13414, col. 2, 2nd para.).

Thus, it would have been obvious to one of skill in the art at the time the invention was made to make a construct encoding a protein operably linked to the αS1-casein regulatory regions as taught by Krimpenfort wherein the protein was Pro-α2(I) collagen. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the protein taught by Krimpenfort with the Pro-α2(I) collagen to produce Pro-α2(I) collagen. One of ordinary skill in the art at the time the invention was made would have recognized that the bovine described by Krimpenfort was a bioreactor and would have been motivated to make any protein in the bioreactor. One of ordinary skill in the art at the time the invention was made would have been motivated to direct expression of human collagen to the mammary gland to prevent a systemic immune response to the human protein. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in obtaining Pro-α2(I) collagen

expression in mammary glands because Krimpenfort obtained exogenous protein expression in mammary glands and because Lee obtained Pro-α2(I) expression in cells that do not normally produce collagen. The combined teachings of Krimpenfort and Lee are no less than the specification which suggests making animals using the method of Krimpenfort (pg 10, line 19) and using the Pro-α2(I) collagen of Lee (pg 13, line 26).

Applicants arguments regarding 103 are generic to all of the 103 rejections. Applicants arguments are not persuasive for reasons addressed above.

9. Claims 2-6 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Krimpenfort (1991, Bio/Technology, Vol. 9, pg 844-847) in view of Khillan (Dec. 5, 1991, J. Biol. Chem., Vol. 266, pg 23373-23379) for reasons of record.

Rein taught a construct comprising a nucleic acid sequence encoding a protein operably linked to the αS1-casein 5' and 3' regulatory regions (pg 39, Fig. 1). The construct was injected into mouse ES cells which were transplanted into pseudopregnant females and transgenic offspring were obtained (sentence bridging pg 39-40). Claim 6 does not require obtaining expression in the mammary gland (see 112/2nd); however, Rein taught obtaining expression of the protein in their mammary gland and isolating the protein from the milk (pg 40, col. 2, line 5-8). Rein did not teach the construct comprised procollagen.

However, Khillan taught a construct encoding the human pro-α1 chain of Type I collagen, transfecting liver cells with the construct and obtaining functional expression of the pro-α1 chain of Type I collagen in transgenic mice.

Thus, it would have been obvious to one of skill in the art at the time the invention was made to make a construct encoding a protein operably linked to the αS1-casein regulatory regions as taught by Rein wherein the protein was the pro-α1 chain of Type I collagen as taught by Khillian. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the protein taught by Rein with the pro-α1 chain of Type I collagen taught by Khillian to produce the pro-α1 chain of Type I collagen in a bioreactor. One of ordinary skill in the art at the time the invention was made would have recognized that the bovine described by Rein was a bioreactor and would have been motivated to make any protein in the bioreactor. One of ordinary skill in the art at the time the invention was made would have been motivated to direct expression of human procollagen to the mammary gland to prevent a systemic immune response to the human protein. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in obtaining Pro-α2(I) collagen expression in mammary glands because Rein isolated exogenous human protein from the milk of transgenic mice and because Khillan obtained human procollagen expression in transgenic mice. The combined teachings of Rein and Khillan are no less than the specification which suggests making animals using methods known in the art and using the pro-α1 chain of Type I collagen.

Applicants arguments regarding 103 are generic to all of the 103 rejections. Applicants arguments are not persuasive for reasons addressed above.

10. Claims 1-6 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Strijker (1992, Conference Proceedings Series, Harnessing biotechnologoy for the 21st century, Ladisch

ed., Publisher: American Chem. Soc. Marketing Division, pg 38-41) in view of Lee (1988, J. Biol. Chem., Vol. 263, pg 13414-13418) for reasons of record.

Strijker taught a construct comprising a nucleic acid sequence encoding a protein operably linked to the αS1-casein 5' and 3' regulatory regions (pg 39, Fig. 1). The construct was injected into mouse ES cells which were transplanted into pseudopregnant females and transgenic offspring were obtained (sentence bridging pg 39-40). Claim 6 does not require obtaining expression in the mammary gland (see 112/2nd); however, Strijker taught obtaining expression of the protein in their mammary gland (pg 844, col. 2, line 7-10). Strijker did not teach the construct comprised procollagen.

However, Lee taught a construct for expressing human Pro-α2(I) collagen, transfecting liver cells with the construct and obtaining functional expression of Pro-α2(I) collagen (pg 13414, col. 2, 2nd para.).

Thus, it would have been obvious to one of skill in the art at the time the invention was made to make a construct encoding a protein operably linked to the αS1-casein regulatory regions as taught by Strijker wherein the protein was Pro-α2(I) collagen as taught by Lee. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the protein taught by Strijker with the Pro-α2(I) collagen to produce Pro-α2(I) collagen. One of ordinary skill in the art at the time the invention was made would have recognized that the bovine described by Strijker was a bioreactor and would have been motivated to make any protein in the bioreactor. One of ordinary skill in the art at the time the invention was made would have been

motivated to direct expression of human collagen to the mammary gland to prevent a systemic immune response to the human protein. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in obtaining Pro-α2(I) collagen expression in mammary glands because Strijker obtained exogenous human protein expression in mammary glands and because Lee obtained Pro-α2(I) expression in cells that do not normally produce collagen. The combined teachings of Strijker and Lee are no less than the specification which suggests making animals using methods known in the art and using the Pro-α2(I) collagen of Lee (pg 13, line 26).

Applicants arguments regarding 103 are generic to all of the 103 rejections. Applicants arguments are not persuasive for reasons addressed above.

***Double Patenting***

The rejection of claims 1, 2 and 6 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,111,165 is withdrawn in view of the terminal disclaimer.

The rejection of claims 1-6 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,111,165 in view of Khillan (Dec. 5, 1991, J. Biol. Chem., Vol. 266, pg 23373-23379) is withdrawn in view of the terminal disclaimer.

The rejection of claims 1, 2 and 6 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5,895,833 is withdrawn in view of the terminal disclaimer.

The rejection of claims 1, 2 and 4-6 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5,895,833 in view of Khillan (Dec. 5, 1991, J. Biol. Chem., Vol. 266, pg 23373-23379) is withdrawn in view of the terminal disclaimer.

The rejection of claims 1-6 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 5,962,648 is withdrawn in view of the terminal disclaimer.

The rejection of claims 1-6 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 5,667,839 is withdrawn in view of the terminal disclaimer.

## *Conclusion*

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

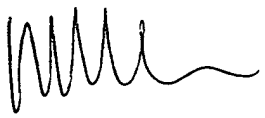
Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson



MICHAEL WILSON
PRIMARY EXAMINER